
IFW

Docket No.: 3893-0219PUS2
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Tore DUVOLD et al.

Application No.: 10/563,103 Confirmation No.: N/A

Filed: December 30, 2005 Art Unit: N/A

For: NOVEL FUSIDIC ACID DERIVATIVES Examiner: Not Yet Assigned

**LETTER**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Subsequent to the filing of the above-identified application on December 30, 2005, attached hereto is an English translation of the International Preliminary Examination Report (Form PCT/IPEA/409) that should be made of record in the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or to credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Dated: April 18, 2006

Respectfully submitted,

By _____
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Attachment(s)

# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

THALSO-MADSEN, Birgit
LEO PHARMA A/S
Patent Section
Industriparken 55
DK-2750 Ballerup
DANEMARK

# PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)* 27.03.2006

Applicant's or agent's file reference
635

**IMPORTANT NOTIFICATION**

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/DK2004/000491 | 09.07.2004 | 16.07.2003 |

Applicant
LEO PHARMA A/S et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
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Authorized Officer

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# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Form PCT/IPEA/416 |
|---|---|---|
| 635 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/DK2004/000491 | 09.07.2004 | 16.07.2003 |

International Patent Classification (IPC) or national classification and IPC

INV. C07J9/00 C07J13/00 C07J51/00 A61K31/575 A61P31/04

Applicant

LEO PHARMA A/S et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☒ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 07.05.2005 | 27.03.2006 |
| Name and mailing address of the international preliminary examining authority: | Authorized officer |
| European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Wörth, C<br>Telephone No. +49 89 2399- |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000491

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   **Description, Pages**

   1-85 as originally filed

   **Claims, Numbers**

   1-35 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000491

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 24-27, 32 and 33 with respect to IA

because:

☒ the said international application, or the said claims Nos. 24-27, 32 and 33 with respect to IA relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000491

## Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-35 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-35 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-23, 28-31, 34, 35 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

## Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

**see separate sheet**

## Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

1. **Re Item I** ***(Basis of the report)***

Reference is made to the following documents:

D1: WO 01/29061 A (DUVOLD TORE ; VON DAEHNE WELF (DK); LEO PHARM PROD LTD (DK)) 26 April 2001 (2001-04-26)

D2: WO 02/070537 A (DUVOLD TORE ; LEO PHARMA AS (DK)) 12 September 2002 (2002-09-12)

D3: WO 02/07707 A (PERICOR SCIENCE INC) 31 January 2002 (2002-01-31)

D4: W. VON DAEHNE ET AL.: "Structure-activity relationships in fusidinic acid-type antibiotics" ADVANCES IN APPLIED MICROBIOLOGY, vol. 25, 1979, pages 95-146, XP009037579

D5: T. DUVOLD ET AL.: "Synthesis and conformational analysis of fusidic acid side chain derivatives in relation to antibacterial activity" JOURNAL OF MEDICINAL CHEMISTRY, vol. 44, no. 19, 2001, pages 3125-3131, XP002299565

2. **Re Item III** ***(Non-establishment of opinion with regard to novelty, inventive step and industrial applicability)***

Claims 24-27, 32 and 33 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

3. **Re Item V** ***(Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement)***

**3.1 Subject-matter**

The present international application relates to

- fusidic acid derivatives of general formula I characterised by a substitution at position C-24 (independent claim 1)
- pharmaceutical compositions containing these compounds (independent claim 21)
- methods of treatment comprising administration of compounds of formula I (independent claims 24, 32 and 33)

- the use of the compounds of formula I for the manufacture of a medicament (independent claim 28)
- a method for the preparation of compounds of formula Ia (characterized by a saturated cyclopenta(a)hydrophenanthrene skeleton (independent claim 34)
- intermediates of formula Ib (independent claim 35) characterised by X being bromo.

### 3.2 Novelty

The subject-matter of present claim 1 differs from D1-D5 in view of present X representing a substituent at C-24.

Claims 2-35 are novel by consequence.

***The requirements of novelty are fulfilled.***

### 3.3 Inventive step

Document D1 is presently considered as closest prior art. This document discloses fusidic acid derivatives (see general formula Ia, page 2) characterised by a modified side chain at position 17 of the cyclopenta(a)hydrophenanthrene skeleton. The compounds of D1 exhibit antimicrobial activity.

In view of this document, the problem to be solved can be regarded as the provision of further fusidic acid derivatives having antimicrobial activity.

The solution provided by the present application consists in fusidic acid derivatives of claim 1 characterised by a C-24 substituent (see definition of present X).

The problem is solved for compounds wherein X represents bromo in view of table A on pages 22-23 of the present specification.

Documents D1-D5 disclose various modifications of the side chain of fusidic acid. In particular, documents D4 (see chapter A) and D5 (see paragraph 'Discussion') disclose structure-activity relationships of fusidic acid analogues with modified side chains. Accordingly, the man skilled in the art would not be surprised to obtain antimicrobial compounds by modifying the substituent at C-24, in particular

by retaining the crucial conformation of the lipophilic moiety of the side chain.

However, the provided solution as exemplified in table A involves an inventive step in view of the unexpected effect of increased activity of the tested compounds against streptococci while essentially retaining the activity against staphylococci vis-à-vis the closest compounds of the prior art.

The breath of the claimed subject-matter with regard to the definition of X appears to be justified in view of the fact that the Applicant has shown for the first time that substitution at C-24 provides an unexpected effect.

The breath of the claimed subject-matter with regard to the definitions of $Q_1$-$Q_3$, G, A-B, Y and Z appears to be corroborated by prior art documents D1-D2.

The subject-matter of claim 35 (intermediates of general formula Ib) is inventive since the claimed intermediates already possess the special 'inventive' feature of the compounds of claim 1 (substitution at C-24).

***The requirements of inventive step are fulfilled.***

3.4 **Industrial applicability**

For the assessment of the present claims 24-27, 32 and 33 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. **Re Item VII *(Certain defects in the international application)***

The requirements of Art. 5 PCT appear to be not fulfilled for the entire subject-matter of claim 1. The application does not contain any indication how to prepare unsaturated fusidic acid derivatives wherein the dotted bonds between C1-C2 and

in the cycplopentane ring or Y and Z represent double bonds. It appears to be questionable that the claimed unsaturated analogues will be obtained according to the process disclosed in the specification and claimed in claim 34 involving a treatment with bromine. The Applicant is invited to submit all information available substantiating that the present application fulfills the requirements of Art. 5 PCT.

5. **Re Item VIII** ***(Certain observations on the international application)***

5.1 The use of the terms 'alkyl', 'alkenyl' and 'aryl' throughout the claims without further qualification renders these claims obscure in scope. Therefore it is not clear whether all compounds implied fall within the scope of the present claims and/or represent a solution of the problem underlying the present application. As chemical species can be defined by the identity and number of atoms involved (see e.g. the definitions given on pages 6-8), the incorporation of the specific substituents given in the specification appears to be necessary for reasons of inventive step and clarity.

5.2 The term "easily hydrolysable ester" in claim 1 does not meet the requirements of clarity in the sense of Art. 6 PCT. The term used is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers. The incorporation of the definition given on page 8, line 5 of the specification appears to be necessary for reasons of clarity.